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SERIAL NO.: 09/460,216, filed December 13, 1999 (Our Docket 50875-F-PCT-US/JPW/AJD)

RE: **Communication Regarding December 7, 2004 Examiner's Interview** in connection with Graham P. Allaway et al., METHODS FOR PREVENTING HIV-1 INFECTION OF CD4+ CELLS, U.S. Serial No. 09/460,216, filed December 13, 1999, including a signed Facsimile Certificate of Mailing dated January 4, 2005.

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Docket No. 50875-F-PCT-US/JPW/AJD

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Graham P. Allaway et al.

Serial No.: 09/460,216 Examiner: Jeffrey S. Parkin

Filed: December 13, 1999 Group Art Unit: 1648

For: METHODS FOR PREVENTING HIV-1 INFECTION OF CD4+ CELLS

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January 4, 2005

Commissioner for Patents
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Sir:

COMMUNICATION REGARDING DECEMBER 7, 2004 EXAMINER'S INTERVIEW

This Communication is submitted pursuant to 37 C.F.R. 1.133(b) to make of record the substance of the discussion between Examiner Jeffrey S. Parkin and applicants during an interview held December 7, 2004 at the U.S. Patent and Trademark Office in connection with the above-identified application. In attendance at the December 7, 2004 interview were Examiner Jeffrey S. Parkin, Dr. Paul J. Maddon (one of the named inventors and Chief Executive Officer of the assignee of record, Progenics Pharmaceuticals, Inc., ("Progenics")), Dr. William C. Olson and Dr. Kathryn M. Brown of Progenics, Ashton J. Delauney, Esq., an associate in the undersigned's law firm, and the undersigned.

The Examiner provided to applicants a written Interview Summary (Form PTOL-413) at the completion of the interview, and a copy thereof was mailed to applicants on December 9, 2004. The present Communication is intended to provide further details of applicants' discussion with the Examiner and thereby complete the record concerning the issues discussed.

Before summarizing the interview, applicants wish to thank Examiner Parkin for the courtesy extended in the interview held December 7, 2004. Applicants understand that the interview was very helpful to the Examiner and are optimistic that the subject application can now be allowed.

Introductory Statements

Applicants' undersigned representative noted that five applications were scheduled for discussion: U.S. Serial Nos. 09/904,356, filed July 12, 2001; 09/460,216, filed December 13, 1999; 09/891,062, filed June 25, 2001; 09/412,284, filed October 5, 1999; and 10/116,797, filed April 5, 2002. Prior to specifically discussing any of these five applications, applicants presented introductory remarks on the scientific background and legal concepts common to all the applications in order to provide an appropriate context for the subsequent discussion of the individual applications.

Overview of Scientific Background

Applicant Dr. Paul J. Maddon then presented an overview of the scientific background concerning the infection process by human immunodeficiency virus (HIV-1) and applicant's role in research thereon. Applicant noted that the HIV-1 infection process occurs in three stages: 1) attachment of HIV-1 through the envelope glycoprotein gp120 to a CD4 receptor on the target cell membrane; 2) fusion of the HIV-1 and target cell membranes after binding to a second receptor (CCR5); and 3) entry of the viral genome into a susceptible target cell mediated by the HIV-1 envelope glycoprotein gp41. Applicant stated that his and his group's contributions to this area of research involved, *inter alia*, the initial cloning of the CD4

gene in the early 1990's; identification of CD4 as the site of attachment for gp120; characterization of the functional distinction between macrophage-tropic and T cell-tropic strains of HIV-1 based on their differential binding to $CD4^+$ cells; identification of CCR5 as the second cell surface receptor mediating fusion of HIV-1 to target cells; and development of a resonance energy transfer (RET) assay to study the process of fusion of macrophage-tropic HIV-1 strains to target cell membranes. It was noted that Progenics was founded, in part, to identify inhibitors of these three stages of HIV-1 infection and to develop such inhibitors as anti-HIV-1 therapeutics. Applicant emphasized the novelty of this therapeutic approach by noting that out of 20 anti-HIV drugs currently on the market, all but one target viral enzymes, e.g., reverse transcriptase and protease, the exception being (Fuzeon®; T-20) which targets viral fusion.

Overview of Legal Concepts

Applicants' undersigned representative then summarized the legal concepts applicable to the cases to be discussed.

Absence of Prior Art

The undersigned noted that because of applicants' pioneering role in the scientific research on which the instant applications were based, there was no prior art being cited in connection with any of the five applications to be discussed. The undersigned also noted that as a consequence of filing early-stage applications soon after making scientific breakthroughs, certain applications may not have had a large number of experimental examples of the inventions, and this was a factor which would be further considered in regard to

the outstanding written description and enablement rejections in certain of the applications. The Examiner acknowledged that prior art was not an issue with respect to the five applications to be discussed.

Legal Standard for Enablement Rejections

The undersigned noted that the Examiner had issued rejections for an alleged lack of enablement in several of the applications. The undersigned also noted that the leading case on enablement, *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), emphasized that the legal standard for lack of enablement is a requirement for undue experimentation, i.e., experimentation that is not routine. In this context, the amount of experimentation required to practice the invention is irrelevant, the critical question being whether the experimentation required is routine. See *In re Wands*, 8 USPQ2d 1400, 1404:

> "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. (citations omitted)

The undersigned noted that *Wands* is a case involving the making of monoclonal antibodies, in which the Federal Circuit reversed an Examiner's initial non-enablement rejection that had been sustained by the Board of Patent Appeals and Interferences on the basis that, whereas considerable experimentation was required, this experimentation involved

routine screening of hybridoma cell lines and hence was not undue experimentation.

The undersigned noted that the RET assay developed by applicants for identifying agents that inhibit fusion of HIV-1 to target cells is highly predictive for agents having the property of inhibiting HIV-1 fusion, and undue experimentation is not required to so identify said agents.

The undersigned acknowledged that not all agents so identified would become drugs useful in treating humans because of considerations such as toxicity and undesirable side effects. The undersigned emphasized, however, that such considerations are irrelevant to patentability and instead are the concern of the Food and Drug Administration (citing *Scott v. Finney* 32 U.S.P.Q. 2d 1115, 1120 [Fed. Cir. 1994]):

> Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA) ... Congress has given the responsibility to the FDA, not to the [PTO], to determine ... whether drugs are sufficiently safe ... (citations omitted)

In addition, the undersigned reminded the Examiner that "it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts ..." *Amgen v. Chugai Pharmaceutical* 927 F.2d 1200, 1213 (Fed. Cir. 1991). The undersigned stated that he hoped to persuade the Examiner that a sufficient number of the *Wand* factors had been satisfied to establish that the specification was enabling for the inventions being claimed.

The undersigned also noted that as part of the enablement rejections, the Examiner had stated that use of the RET assay to identify fusion inhibitors does not constitute rational drug design. The undersigned agreed, noting that in the pharmaceutical industry, "rational drug design" is not the norm. Instead, the historical norm for identifying new candidate drugs is screening of large numbers of compounds. The undersigned noted that, in fact, it is only within the past ten years or so that Agouron Pharmaceuticals, Inc. (now part of Pfizer, Inc.) had successfully developed and marketed the first drug based on rational drug design.

The undersigned also noted that the Examiner had sometimes cited in his enablement rejections a lack of disclosure about the mechanism of action of a drug. The undersigned asserted, however, that disclosure of a mechanism is not a requirement for patentability. In response, the Examiner commented that it helps if the mechanism is disclosed, but acknowledged that disclosure of a mechanism is not required.

The undersigned also pointed to the fact that a single example of an embodiment of the invention may suffice to show enablement provided that "any gaps between the disclosures and the claim breadth could be easily bridged." *Amgen v. Hoechst* 314 F.3d 1313, 1336 (Fed. Cir. 2003). In this context, the undersigned stated that the instant applications and expert declarations previously submitted provide many examples of HIV-1 fusion inhibitors including chemokines, antibodies, and small molecules.

Examiner Must Consider Expert Declarations

The undersigned noted that in three of the applications under consideration, expert declarations had been submitted to support applicants' arguments in response to written description and enablement rejections, two each in two applications and one in the third. The undersigned emphasized that the Examiner is required to consider and give weight to these expert declarations, and if the statements therein are rejected, specific reasons have to be provided by the Examiner for rejecting them (citing M.P.E.P. §2164.05 and *In re Alton*).

> Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); *cf. In re Alton*, 76 F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered)...
> The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. (emphasis in original) M.P.E.P. §2164.05.

See also *In re Alton*, 37 U.S.P.Q.2d 1578, 1582 (Fed. Cir. 1996):

> ... the examiner's final rejection and Answer contained two errors: ... (2) the summary dismissal of the

> declaration, without an adequate explanation of why the declaration failed to rebut the Board's *prima facie* case of inadequate written description.

However, the undersigned noted that in many cases the Examiner had summarily dismissed applicants' declarations, seemingly on the basis of a difference of opinion between the Examiner and the declarants.

Utility of Post-Filing Date References

The undersigned further noted that in response to the enablement rejections, applicants and/or the experts who submitted declarations had cited post-filing date references demonstrating that applicants and others had used the RET assay, as disclosed in the specification, to identify inhibitors of HIV-1 fusion. The undersigned also noted that the Examiner had invariably failed to consider these references on the ground that they had been published after the application filing date. The undersigned quoted the Examiner's April 20, 2004 Office Action in connection with U.S. Serial No. 09/460,216:

> Applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. (citations omitted)

The undersigned stated that he fully agreed with this statement but noted that the post-filing date publications had not been used to show what was known at the time of filing. Rather, these publications had been submitted as evidence that the disclosures in the specification as filed are sufficient

to enable a person skilled in the art to practice the invention being claimed without undue experimentation, i.e., to demonstrate that the disclosure was enabling as of the filing date. The undersigned noted that several Federal Circuit decisions confirm the utility of post-filing date references for this purpose, for example, *Gould v. Quigg* 3 U.S.P.Q.2d 1302 (Fed. Circ. 1987):

> As to the technical article, it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case, the later dated publication was not offered as evidence for this purpose. Rather, it was offered as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative. ... It was not legal error for the district court to accept the testimony of an expert who had considered a later publication in the formulation of his opinion as to whether the disclosure was enabling as of the time of the filing date of the '540 application. *Gould v. Quigg* 3 U.S.P.Q.2d 1302, 1305.

Rebuttal of *Prima Facie* Case of Non-Enablement

The undersigned noted that the initial burden is on the Examiner to make a *prima facie* case of non-enablement. The undersigned stated that applicants did not think the Examiner had made out a *prima facie* case in the applications to be discussed, but even assuming he had done so, applicants are entitled to rebut such a *prima facie* case. It was noted that the Examiner is then required to respond to applicants' rebuttal with specificity. The undersigned maintained that applicants had rebutted the Examiner's findings of lack of enablement by argument and, in some instances, by filing expert declarations. The undersigned reiterated that, in response, the Examiner had not given due weight to the submitted declarations (citing M.P.E.P. §2164.05; *In re Alton*)

and, contrary to *Gould v. Quigg*, had invariably dismissed evidence of enablement based on post-filing date publications.

Grouping of Applications for Discussion

The undersigned stated that U.S. Serial Nos. 09/904,356, 09/460,216, 09/891,062 and 09/412,284 would be grouped together (Group I) for discussion, separate from U.S. Serial No. 10/116,797 (Group II). The undersigned noted that the Group I applications are related in that they involve methods for inhibiting HIV-1 fusion using an agent that binds to the CCR5 coreceptor, which agent is identified by the RET assay, although CCR5 is not referred to by name in U.S. Serial Nos. 09/904,356, 09/891,062 and 09/412,284. The undersigned also stated, however, that differences observed in the inhibition of fusion of macrophage-tropic versus T cell-tropic HIV-1 strains with PM-1 target cells were later discovered by applicants to be due to binding of the inhibitor to CCR5 which is the coreceptor for macrophage-tropic HIV-1 strains.

The undersigned noted that the CCR5 coreceptor is specifically referred to in U.S. Serial No. 09/460,216, and further noted that in U.S. Serial Nos. 09/891,062 and 09/412,284, the agent is a monoclonal antibody. The undersigned noted that the Examiner had rejected the claims in these Group I applications on the grounds of inadequate written description and lack of enablement.

The undersigned noted that U.S. Serial No. 10/116,797 in Group II was separate from the Group I applications to the extent that it is a later application which discloses specific monoclonal antibodies that bind to CCR5 and inhibit HIV-1 infection. The undersigned also noted that the claimed

invention is directed to reducing HIV-1 viral load in an HIV-1 infected subject and that the issues raised in this application are less complex than in the Group I applications. The undersigned stated that amended claims had been drafted in connection with U.S. Serial No. 10/116,797, which were believed to obviate the Examiner's grounds of rejection in the October 6, 2004 Office Action. In this regard, the undersigned noted that draft claims for the Examiner's consideration had been forwarded to him by facsimile and e-mail on December 6, 2004. The Examiner acknowledged that he had received these draft claims.

Discussion of the Subject Application (Serial No. 09/460,216)

The subject application was the second application discussed during the interview following the discussion of U.S. Serial No. 09/904,356.

The undersigned noted that claim 61 is the only claim pending in the subject application. The undersigned also noted that claim 61 had been amended in applicants' October 20, 2004 Amendment filed in response to the April 20, 2004 Office Action. The undersigned further noted that the invention is directed to a method of inhibiting infection of a CD4+ cell by a macrophage-tropic HIV-1, which method comprises contacting the CD4+ cell with an agent (a) capable of binding to a CCR5 chemokine receptor on the surface of the CD4+ cell; (b) capable of blocking fusion of $HIV\text{-}1_{JR\text{-}FL}$ with a PM-1 cell; and (c) not capable of blocking fusion of $HIV\text{-}1_{BRU}$ with such PM-1 cell, in an amount and under conditions such that the fusion of the macrophage-tropic HIV-1 or a macrophage-tropic HIV-1-infected cell to the CD4+ cell is inhibited, so as to thereby inhibit infection of the CD4+ cell by the macrophage-tropic

HIV-1. The undersigned also noted this application is one of the applications to be discussed which specifically defines the HIV-1 coreceptor as CCR5.

The undersigned noted that the specification ~~discloses~~ exemplifies two different classes ~~of examples~~ of HIV-1 fusion-inhibitory agents that meet the limitations of the claims, i.e., chemokines and antibodies. The specification further discloses that nonpeptidyl agents may also inhibit infection as claimed. The undersigned further noted that within the antibody class, the specification discloses several examples, namely, monoclonal antibodies PA8, PA9, PA10, PA11 and PA12 which satisfy the claim limitations. The undersigned also noted that, by comparison, the previously discussed U.S. Serial No. 09/904,356 discloses monoclonal antibodies PA3, PA4, PA5 and PA7 which are earlier antibodies in the series of HIV-1 fusion-inhibiting monoclonal antibodies isolated by applicants. The undersigned additionally noted that applicants have already been issued a patent (U.S. Patent No. 6,344,545, issued February 5, 2002) containing claims directed a similar method of inhibiting infection of a CD4+ cell but that the claims in the issued patent are limited to an anti-viral agent which is an anti-CCR5 antibody.

The Examiner reviewed the two expert declarations of Dr. Tatjana Dragic which had previously been submitted by applicants on March 31, 2002 and August 26, 2003 to address the enablement of nonpeptidyl agents. The Examiner stated that in the normal course of examining applications, examiners had very little time to review declarations in detail. He further stated that because of this time limitation, he appreciated the opportunity to meet with the inventors and

discuss the applications in detail as in the present interview session.

The undersigned noted that in the April 20, 2004 Office Action, the Examiner had stated that "the disclosure fails to provide any guidance pertaining to the three-dimensional configuration of the CCR5 receptor. Thus, the skilled artisan can not employ a rational drug-screening strategy."

In response, the undersigned stated that the CCR5 gene had been cloned and thus its amino acid sequence had been known (citing M. Samson et al. [1996] Molecular cloning and functional expression of a new human CC-chemokine receptor gene. Biochemistry 35: 3362-3367) before the priority date of the subject application. The undersigned emphasized that one skilled in the art could therefore readily make the CCR5 polypeptide and raise antibodies against it without undue experimentation. Accordingly, the undersigned maintained that a knowledge of the three-dimensional structure of CCR5 is not required to practice the claimed invention.

In response, the Examiner stated that the claimed antibody is required to bind to a trimolecular complex and, thus, obtaining antibodies which meet the claim limitations is not as simple as injecting CCR5 protein into a rabbit and thereby raising antibodies.

Dr. William Olson respectfully pointed out to the Examiner that, in fact, the antibodies disclosed in the specification and which meet the claim limitations bind just to CCR5, and not to the trimolecular complex. The Examiner then acknowledged that binding to just CCR5, as compared to binding to the trimolecular complex, simplified the requirements for

making the antibody. The Examiner suggested that applicants should mention in a subsequent communication that the structure of CCR5 was known by the priority date of the subject application.

With reference to the Examiner's statement about not being able to employ a rational drug-screening strategy, the undersigned reiterated that rational drug design is not the norm in the development of new drugs. The undersigned further noted, however, that the specification provides a rational strategy in identifying inhibitors of HIV-1 infection based on the RET assay. In this regard, the undersigned directed the Examiner's attention to the two declarations of Dr. Dragic which emphasized the efficacy of the RET assay in identifying agents that inhibit HIV-1 infection of CD4+ cells, even without any prior knowledge of the chemical structures of these agents, and without undue experimentation. See paragraphs 8-17 of the March 31, 2002 declaration and paragraphs 9-11 of the August 26, 2003 declaration of Dr. Dragic.

The undersigned also directed the Examiner's attention to the descriptions in Dr. Dragic's second declaration of the use of applicants' RET assay by Hoffmann-La Roche AG ("Roche") to identify small nonpeptidyl compounds that inhibit HIV-1 infection. See paragraphs 6 and 11 of the August 26, 2003 declaration of Dr. Dragic. It was noted that Roche had filed a patent application (PCT International Publication No. WO 02/079186 A2) claiming these compounds *per se* and their use in preventing cell infection by HIV-1.

The Examiner inquired as to the identity of the small molecule inhibitors identified by Roche. In response, Dr. William

Olson stated that they were aminopiperidine derivatives (citing WO 02/079186 A2).

The undersigned also directed the Examiner's attention to the statements in Dr. Dragic's second declaration concerning the SCH-C product of Schering-Plough Corporation. See paragraphs 13-15, 17 and 18 of the August 26, 2003 declaration of Dr. Dragic. SCH-C is a non-peptidyl agent which has demonstrated potent anti-HIV-1 activity in the clinic and which applicants have also shown is active in the RET assay in inhibiting HIV-1 fusion to target cells.

The Examiner stated he found Dr. Dragic's declarations very useful because they show that applicants can point to different classes of compounds, for example, TRO140 which is a humanized antibody, and small organic molecules as identified by Roche and Schering-Plough, as multiple examples of agents which inhibit HIV-1 infection. The undersigned urged that these multiple species support the generic agent language recited in the claims.

The undersigned stated that the key question to be addressed is the legitimacy of using post-filing date publications to support enablement of the claims in the specification as filed.

In response, the Examiner stated that he has no objections to the use of post-filing date publications in the present context.

The Examiner stated that he would discuss applicants' remarks arguments with his Supervisory Patent Examiner. The Examiner also stated that following this discussion with his

supervisor, he would provide guidance to applicants whether pending claim 61 is allowable or whether allowance would be dependent upon any further amendment(s).

Conclusion

Applicants respectfully request that the Examiner, in consultation with his Supervisory Patent Examiner, consider applicants' remarks in their October 20, 2004 Amendment in light of the discussion summarized above. Applicants maintain that their arguments made in the October 20, 2004 Amendment and hereinabove obviate the grounds of rejection set forth in the April 20, 2004 Office Action.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being transmitted via facsimile on this date to:

Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

1/4/05

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